

### **DETAILED ACTION**

Claims 1, 18, 29-33 and 37 are pending.

Inspection of the record indicates that the Office Action mailed on May 27, 2010 should have been a Non-Final Office Action.

An amendment in response to said Office Action dated May 27, 2010 was filed October 27, 2010.

As such, the notice of abandonment mailed February 3, 2011 and Advisory Action mailed November 12, 2010 are hereby withdrawn.

This Office Action in response to Amendment filed October 27, 2010 is set forth below.

Claims 1, 18, 29-33 and 37 are being acted upon in this Office Action.

### **Rejection Remains**

#### **Claim rejection under - 35 U.S.C. 112**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 18, 29 and 31 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. **This is New Matter.**

The recitation of antibody or binding fragment thereof which binds to an MHC class II molecule in claim 1 has no written support in the specification and the claims as originally filed.

The recitation of antibody or binding fragment which binds to an MHC class II molecule in claim 18 has no written support in the specification and the claims as originally filed.

The specification discloses the first sequence comprises a polypeptide which is capable of binding to another APC surface molecule. Such APC molecules include: CD205 (DEC205), CD204 (Scavenger receptor), CD14, CD206 (Mannose receptor), TLRs, Langerin (CD207), DC-SIGN (CD209), Fc, receptor 1 (CD64) and Fc, receptor 2 (CD32), CD68, CD83, CD33, CD54 and BDCA-2,3,4, see page 13, line 5-9.

It will be appreciated that the first sequence may therefore take the form of an antibody to an APC surface molecule. In a preferred embodiment the antibody is generated against the APC extracellular domain of the APC surface molecule, or a fragment thereof. The production of antibodies is described in for example Kohler and Milstein (1975) Nature 256:495-497, see page 13, lines 11-15.

The specification discloses superantigen as a first polypeptide that binds to MHC class II, see page 13, lines 1-3. As such, the specification does not describe antibody to MHC class II molecule, much less binding fragment thereof that bind to MHC class II molecule on the surface of antigen representing cell (APC).

With respect to claim 29, the specification does not adequately describe the polypeptide comprising the six CDRs of any antibody or binding fragment thereof that binds to MHC class II molecule, CD205 (DEC205), CD204 (Scavenger receptor), CD14, CD206 (Mannose receptor), TLRs, Langerin (CD207), DC-SIGN (CD209), Fc, CD68, CD83, CD33, CD54 and BDCA-2,3,4 in the claimed fusion protein. As such, it follows that the polynucleotide sequence encoding such antibody or binding fragment thereof fused to SEQ ID NO: 40, or SEQ ID NO: 42 or SEQ ID NO: 43 or SEQ ID NO: 44 is not adequately described.

Applicants' arguments filed October 27, 2010 have been fully considered but are not found persuasive. Applicant's position is that the specification recites that the first sequence may comprise "a polypeptide that is capable of binding to a MHC class II molecule." Specification, p. 12, 11.17-19. The specification also indicates the first sequence may "take the form of an antibody to an APC surface molecule." *Id.*, p.13, 11.12-13. Given that a MHC class II molecule is an APC surface molecule, the skilled artisan would recognize that the specification supports an antibody (or binding fragment thereof) that binds to an MHC class II molecule.

Contrary to applicants' assertion that that the specification indicates the first sequence may take the form of antibody to an APC surface molecule such as MHC class II molecule, the paragraph at page 12 reproduces below:

"The first sequence is capable of targeting a second sequence to an APC for presentation to a TCR. In a preferred embodiment the first sequence comprises a polypeptide that is capable of binding to a MHC class II molecule. Preferably the first sequence is or is derived from a superantigen and comprises the MHC class II molecule binding domain thereof. Preferably the first sequence does not include the TCR binding domain of the superantigen.", see page 12, lines 16-21.

Said paragraph discloses that the first sequence that binds to MHC class II molecule is a superantigen, not an antibody as argued. Furthermore, the specification at page 13 discloses "In another embodiment the first sequence comprises a polypeptide which is capable of binding to another APC surface molecule. Such APC molecules include: CD205 (DEC205), CD204 (Scavenger receptor), CD14, CD206 (Mannose receptor), TLRs, Langerin (CD207), DC-SIGN (CD209), Fc, receptor 1 (CD64) and Fc, receptor 2 (CD32), CD68, CD83, CD33, CD54 and BDCA-2,3,4."

"It will be appreciated that the first sequence may therefore take the form of an antibody to an APC surface molecule. In a preferred embodiment the antibody is generated against the APC extracellular domain of the APC surface molecule, or a fragment thereof. The production of antibodies is described in for example Kohler and Milstein (1975) Nature 256:495-497." Again, there is no mention of MHC molecule and antibody that binds to such.

Finally, the claims and the specification as originally filed fail to provide written support for the claimed limitation of antibody or binding fragment thereof that binds to MHC class II molecule other than superantigen TSSI. No amendment shall introduce new matter into the claims. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981). For these reasons, the rejection is maintained.

### **Claim Rejections - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 18, 29, 31 and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 7,030,228 B1 (filed November 15, 2000; PTO 892) in view of US application 2005/0137130 A1 (filed May 14, 2004; PTO 892).

The '228 patent teaches fusion protein comprising an antibody such as anti-BDCA-2 or anti-BCDA-3 or anti-BDCA-4 or binding fragment thereof such as Fab and F(ab')<sub>2</sub> as the first polypeptide that binds to an APC surface molecule such as BDCA-2 or BCDA-3 or BDCA-4, respectively, wherein the antibody or binding fragment thereof is fused to a second polypeptide or an effector molecule such as cytokine or toxin (see col. 16, lines 64-67, col. 17, Table 1, col. 19, lines 16 through col. 20, lines 1-13, col. 21, lines 11-32, in particular). The reference fusion protein is useful for targeting the drug of interest to antigen presenting cells (see col. 16, lines 51-56, in particular). The '228 patent teaches a composition

comprising the reference fusion protein and pharmaceutical acceptable carrier (see col. 37, line 60 through col. 38, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the fusion protein wherein the second polypeptide is human Delta 1 comprising the amino acid sequence of SEQ ID NO: 40.

The US application 2005/0137130 teaches human Delta 1 comprising the amino acid sequence of SEQ ID NO: 51, which is 100% identical to the claimed SEQ ID NO: 40 (see reference SEQ ID NO: 51, Figure 4A, in particular). The reference second sequence Notch ligand comprises DSL domain and at least one EGF-like repeat, See Figure 5, in particular. The publication further teaches human notch ligand fragment consisting of residues 159-221, which is 100% identical to the claimed fragment of SEQ ID NO: 25 (see Figure 5, DLL1Human/159-221, in particular). The advantage of using such soluble Notch ligand is that it provides effective inhibition of Notch signaling with little or no competing agonist activity and such polypeptide may also be easier to produce in bacterial expression system (see paragraph 0094, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cytokine or toxin in the fusion protein comprising antibody or binding fragment thereof that binds to BDCA-2, BDCA-3 or BCDA-4 of the '228 patent for the Delta 1 comprising the amino acid sequence of SEQ ID NO: 51 or fragment thereof as taught by the US application 2005/013710. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do substitute one known effector molecule for another known effector molecule because US application 2005/0137130 teaches human Delta 1 or fragment thereof is effective for inhibition of Notch signaling with little or no competing agonist activity and such polypeptide may also be easier to produce in bacterial expression system (see paragraph 0094, in particular).

One having ordinary skill in the art would have been motivated to fuse any one of the antibody such as anti-BDCA-2 or anti-BCDA-3 or anti-BDCA-4 or binding fragment thereof such as Fab, F(ab')<sub>2</sub> to the human Delta 1 or fragment thereof because the antibody or binding fragment thereof in the fusion protein is useful for targeting the drug of interest to antigen presenting cells by binding to BDCA expressed on antigen presenting cells thereby eliminating some of the toxicity and less dose is needed as a pharmaceutical composition (see col. 16, lines 51-56, in particular). Claim 29 is included in this rejection because the reference fusion protein is made recombinantly by transforming host cell such as E coli with

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an expression vector such as pET-22b comprising a polynucleotide encoding the fusion protein as taught by the '228 patent (see col. 24, line 33 through 56, in particular).

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

- A) Combining prior art elements according known methods to yield predictable results.
- B) Simple substitution of one known element for another to obtain predictable results.
- C) Use of known technique to improve similar products in the same way.
- D) Applying known technique to a known product ready for improvement to yield predictable results.
- E) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.
- F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, combining prior art elements according known method would yield predictable results. Simple substitution of one known element cytokine or toxin in fusion protein for another effector molecule human Delta 1 would obtain predictable results.

Obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed October 27, 2010 have been fully considered but are not found persuasive. Applicant's position is that based on the teachings of the '130 publication, one of ordinary skill in the art would understand human Delta 1 to be used in the '130 publication as an inhibitor of Notch signaling. See, e.g., '130 publication, 0066-67, 0070-71, 0094,1099-1102. However, this teaches away from the instant claims that recite that the second sequence or the Notch ligand (or a fragment thereof) retains Notch signaling activity. Thus, the '130 publication teaches away from the claimed invention. In

addition, the skilled artisan could not have predicted, based on the teachings in the '130 publication, that the second sequence or Notch ligand of the invention would retain Notch signaling activity.

In response, the notch ligand of the '130 publication comprises the amino acid sequence of SEQ ID NO: 51, which is 100% identical to the claimed SEQ ID NO: 40 in the second sequence of the claimed fusion protein. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. In this case, if applicant's second sequence, i.e., Notch ligand comprising the amino acid sequence of SEQ ID NO: 40 retains Notch signaling activity, so is the reference notch ligand which comprises the exact amino acid sequence (see reference SEQ ID NO: 51). If the reference Notch ligand does not retain Notch signaling activity, neither is applicants' Notch ligand. With respect to the argument that the '130 publication teach inhibitor of Notch signaling, while the '130 publication teaches the reference fragment has inhibitory activity of Notch signaling, the full-length sequence of SEQ ID NO: 51 still retains Notch signaling activity because the terms "or" and "selected from the group consisting of" are recited in claim 1. The recitation of the "second sequence retains Notch signaling activity" is in item (iii). The Notch ligand comprising the amino acid of SEQ ID NO: 40 in item (ii) and does not require retaining Notch signaling activity as argued. For these reasons, the rejection is maintained.

No claim is allowed.

**THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/

Primary Examiner, Art Unit 1644